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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,036	12/15/1998	JOCHEN MAURER	P564-8019	1165

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/147,036	MAURER ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,19,41 and 43-59* is/are pending in the application.

4a) Of the above claim(s) *4-8 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-15, 19, 41, 43-53 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed July 26, 2004. Claims 1, 3 9-10, 14, 19, 41, 45, 55, 57 and 59 have been amended. Claims 16-17, 20-40 and 42 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections Withdrawn

3. In view of Applicant's amendment the following Objections and Rejections have been withdrawn:

a) Objection to the specification, page 3, paragraph 4, of previous Office action.

b) Objection to the specification, page 3, paragraph 5, of previous Office action.

c) Objection to the claims, page 3, paragraph 6, of previous Office action.

d) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 11, paragraph 9 (a) of previous Office action.

e) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 11, paragraph 9 (c) of previous Office action.

f) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 11, paragraph 9 (d) of previous Office action.

g) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 11, paragraph 9 (e) of previous Office action.

h) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 11, paragraph 9 (f) of previous Office action.

Rejections Maintained

4. The rejection under 35 U.S.C. 112, first paragraph, (biological deposit) is maintained for claims 1-3, 9-15, 19, 41, 43-53 and 55 –59 for the reasons set forth pages 4-7 paragraph 7 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a process for presenting passenger peptides or polypeptides on the surface of gram-negative bacteria, a process of obtaining a library of bacteria expressing a variant population of surface-exposed passenger peptides or polypeptides, a recombinant vector and a recombinant gram-negative host bacterium.

Because it is not clear that cell lines possessing the properties of a gram-negative host cell comprising a variant of the *E. coli* transporter domain of the AIDA protein are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of a suitable deposit for patent purposes a deposit in a public repository is required. Without a publicly available deposit of the above gram-negative host cell, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the gram-negative host cell in the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met. If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;
(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;
(c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the repository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit. If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the gram-negative host cell described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Applicant urges that the Examiner is incorrect in requiring a biological deposit, particularly one comprising a variant. Applicant urges that an Applicant need not

guarantee that every aspect of the specification by precisely reproducible but rather the best mode and an adequate means of carrying out the invention be described. Applicant urges that the genetic material obtained from generally available sources is being inserted into a host cell that is also obtained form generally available sources as the specification makes clear in various place.

Applicant's arguments filed July 26, 2004 have been fully considered but they are not persuasive. Applicant is claiming a process for presenting a passenger peptide or polypeptide on the surface of a gram-negative host bacteria which requires that the host cell be transformed with a vector comprising various DNA sequences. The mere fact that the components used in the process are generally publicly available does not mean that the skilled artisan could practice the claimed invention since Applicant uses variant sequences as part of the claimed process. It must be remembered that 35 U.S.C. 112, first paragraph requires that the Applicant must describe how to make and use the claimed invention. A biological deposit of the gram-negative bacteria host is required because the bacterial host has been modified to have characteristics that are specific to the claimed process. Therefore, this rejection is maintained.

5. The rejection under 35 U.S.C. 112, first paragraph, (enablement) is maintained for claims 1-3, 9-15, 19, 41, 43-53 and 55-59 for the reasons set forth pages 8-10 paragraph 8 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for presenting passenger peptides or polypeptides on the surface of gram-negative host bacteria, wherein the transporter domain is an Adhesin Involved in Diffuse Adherence (AIDA) protein of *E. coli*, does not reasonably provide enablement for process for presenting passenger peptides or polypeptides on the surface of gram-negative host bacteria, wherein the transporter domain is a variant of the AIDA protein of *E. coli* or variant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the C-terminal domain of the AIDA protein, the AIDA autotransporter serves as a membrane anchor for the presentation of recombinant antibody domains on the surface of gram-negative bacteria (page 13). The specification teaches in experimental examples 1 and 2 that the natural surface protein of *E. coli* was chosen for the invention, which was the AIDA protein of *E. coli* (page 33). The specification teaches that the sequence of this protein is known (page 33).

The prior art, for example, Benz et al (*Infection and immunity, May 1989, p. 1506-1511)* teach that the biochemical properties of ADIA are still under investigation (page 1511). Benz et al (*Molecular Microbiology, 1992, 6(11), 1539-1546)* teach that the adherence mechanisms of enterpathogenic *E. coli* to epithelial cells is not understood (see the Summary).

The instant specification does not teach or define a structure for variants of the AIDA protein. There is no guidance provided as to which amino acids can be added, deleted or substituted and the AIDA protein would retain its biological function. The scope of the claims is not commensurate in scope with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what

changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting variants of the AIDA protein having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use variants of the AIDA protein in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicant urges that the gram-negative host bacteria recited in the claims can be produced from known material without under experimentation, based on the description and teachings of the specification. Applicant urges that the specification teaches one skilled in the art how to modify the sequence of the AIDA-I protein to maintain biological function. Applicant refers to several pages in the specification to support their position. Applicant urges that variants of the E. coli AIDA protein have 80% homology to the AIDA-1 autotransporter domain in least their β-sheet regions. Applicant urges that the claimed invention is fully enabled by the specification.

Applicant's arguments filed July 26, 2004 have been fully considered but they are not persuasive. Applicant is claiming a process for presenting passenger a peptide or polypeptide on the surface of a gram-negative host bacteria which requires that the host cell be transformed with a vector comprising various DNA sequences. The Examiner has reviewed that instant specification including the pages of the specification cited by Applicant and has not found support for the recitation "having a homology of at least 80% of the AIDA-1 autotransporter domain in at least its β-sheet regions". The instant specification does not teach one of skill in the art to make and use the claimed invention. There is no guidance in the specification as to how one skilled in the art would obtain the variants used in the claimed process. The instant specification does not teach or define a structure for variants of the AIDA protein. There is no guidance provided as to which amino acids can be added, deleted or substituted and the AIDA protein would retain its biological function. The scope of the claims is not commensurate in scope with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. It should be remembered that 35 U.S.C. 112 first paragraph requires that Applicant teaches how to make and use the claimed invention not how to find "variants that have at least "80% of the AIDA-1 autotransporter domain in at least its β-sheet regions". The structure for the variants are required for the claimed process. Therefore, Applicant has not meet the burden required under 35 U.S.C. 112, first paragraph. Thus the claimed process is not enabled.

6. The rejection under 35 U.S.C. 112, second is maintained for claim 1 for the reasons set forth page 11 paragraph 9(b) of the previous Office Action.

The rejection was on the grounds that the claims is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Correction and/or clarification is required. Claim 1 recites "under conditions". It is unclear as to what applicant is intends?

Applicant urges that one of ordinary skill in the art would clearly understand what is meant by this term as use in the claims. Applicant urges that one skilled in the art would know what conditions are commonly used to cultivate such bacteria to induce expression of the recited polynucleotide and the presentation of the passenger peptide on the surface of a bacterium.

Applicant's arguments filed July 26, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that the term "under conditions" is unclear and indefinite. The claimed process comprises the uses of gram-negative hosts which encompasses all gram-negative host from the genera *Escherichia, Serratia* and *Rickettsia* to name a few that have different culture conditions. It should also be remembered that the claimed process comprises culturing various gram-negative host and transforming the host with various DNA sequences to present the passenger peptides to the surface. Hickman et al *(Microbial Pathogenesis, 1991, 11, 19-31)* teach that *Rickettsia tsutsugamushi* are cultured at 34°C on L-929 cells in a 5% CO_2 humidified atmosphere (page 28). Hickman et al teach that *E. coli* were grown on Luria broth agar. *Maurer et al, 1997, (Journal of Bacteriology, 1997, 794-804)* teach

that *E. coli* are cultured at 37°C in Luria agar. Therefore, different gram-negative organisms may require different conditions just as they required various culture conditions. Therefore, this rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Objection

7. Claim 1 is objected to for the following informality: the term "peptides" should be changed to "peptide" and the term "polypeptides" should be changed to "polypeptide" since the process is directed to presenting one passenger peptide or polypeptide on the surface of a gram-negative bacteria.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Newly amended claims 1-3, 9-15, 41, 43-53 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* The amendment filed July 26, 2004 introduced new matter into the claims.

Claims 1-3, 9-15, 41, 43-53 and 55-59 introduce new matter because they recite "... a variant having a homology of at least 80% of the AIDA-1 autotransporter domain in at least its β-sheet region" which is not disclosed, taught or supported in the instant specification. Applicant has failed to direct the Examiner as to where in the instant specification the support for this amendment is specifically shown or implied. The Examiner has reviewed the instant specification and has failed to find the support for the amendment. Removal of the phrase "a variant having a homology of at least 80% of the AIDA-1 autotransporter domain in at least its β-sheet region" from the claims is requested.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15 and 19 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 15 and 19 recite "...libraries of variant passenger peptides or polypeptides are expressed in host cells...". It is unclear how libraries are produced when claim 1 (the independent claim from which claims 15 and 19 depend) is a process of presenting one peptide or polypeptides to on the surface of a gram-negative host. Correction and/or clarification is required.

Status of Claims

10. No claims allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272–0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
October 30, 2004

NITA MINNIFIELD
PRIMARY EXAMINER
11/1/04